Kidney International, Vol. 67 (2005), pp. 813–821

PERSPECTIVES IN BASIC SCIENCE

Role of macromolecular IgA in IgA nephropathy

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Role of macromolecular IgA in IgA nephropathy. Primary IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis, leading to progressive renal failure in almost one third of the patients. The disease is characterized by mesangial deposits of IgA. The pathogenesis of IgAN remains incompletely understood. The basic abnormality of this disorder lies within the IgA immune system rather than in the kidney. Elevated levels of IgA and IgA-containing complexes are found in sera of most patients with IgAN, but increased levels alone are not sufficient to develop IgAN. Therefore abnormal physicochemical properties of circulating IgA, such as size, charge, and glycosylation may play a role. This is supported by the presence of altered glycosylation of serum and mesangial IgA in patients with IgAN. Although the precise origin and nature of the mesangial IgA deposits are still uncertain, they contain at least in part macromolecular IgA, which may be derived from circulating IgA-containing complexes. Recently, novel insights have been obtained in the molecular composition of circulating high-molecular-weight IgA, which might include complexes with underglycosylated IgA1 and IgA-CD89 complexes. In this review various aspects of macromolecular IgA in relation to IgAN will be discussed.

Primary IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis with a variable spectrum of clinical presentations, leading to progressive renal failure in almost one third of the patients [1, 2]. The disease is characterized by mesangial deposits of IgA and C3, although IgG and less frequently IgM may also be codeposited. The mesangial IgA is of the IgA1 isotype although in a few cases codeposition of IgA2 has been observed.

IgAN is typically diagnosed in young adults, males more commonly affected than females. About 40% of cases have recurrent episodes of macroscopic hematuria, frequently preceded 1 or 2 days earlier by infections. In the majority of patients, the disease has an indolent course manifested by persistent or intermittent microscopic hematuria. Rapidly progressive renal failure is an uncommon event, but acute renal failure (ARF) can develop in individual cases either on the basis of crescentic glomerulonephritis or on the basis of renal tubular obstruction by red blood cells [3]. On follow-up mild proteinuria usually develops which may progress to heavy proteinuria in the nephrotic range. Proteinuria frequently precedes the development of hypertension [4, 5]. The level of proteinuria, the severity of hypertension, and the degree of microscopic hematuria are indicators of progression of the disease, manifested by progressive loss of glomerular filtration rate (GFR) [6].

The pathogenesis of this disease remains incompletely understood. Reports of recurrent IgA deposits in normal kidneys transplanted in recipients with IgAN provide evidence that the basic abnormality in this condition lies within the IgA immune system rather than in the kidney [7]. This is further strengthened by the observation that the IgA deposits disappear when a graft containing mesangial IgA deposits is accidentally transplanted in recipients not suffering from IgAN [8]. The clinical association between exacerbations of the disease and mucosal infections has promoted the view that IgAN is connected with the mucosal immune response. Further, physicochemical properties, like abnormal glycosylation of serum IgA1 are thought to play an important role in the pathogenesis of mesangial IgA deposition.

Although the origin and nature of the IgA deposits remains uncertain, the mesangial IgA has been found to consist at least in part of macromolecular IgA [9, 10]. In this review several aspects of macromolecular IgA in relation to IgAN will be discussed.

IMMUNOGLOBULIN A

The human IgA immune system consists of two compartments: the mucosa-associated lymphoepithelial tissue (MALT) and the bone marrow-plasma compartment [11, 12]. The IgA molecule is a tetramer, consisting of two identical light (κ or λ) and two heavy (α) chains. It occurs in two isotypic forms, IgA1 and IgA2. IgA is produced in higher quantities than all other isotypes combined, with the mucosal immune system as the main production site. In contrast to other immunoglobulins,

Key words: IgA, IgA nephropathy, macromolecular IgA, polymeric IgA.

Received for publication February 18, 2004
and in revised form May 26, 2004
Accepted for publication October 21, 2004

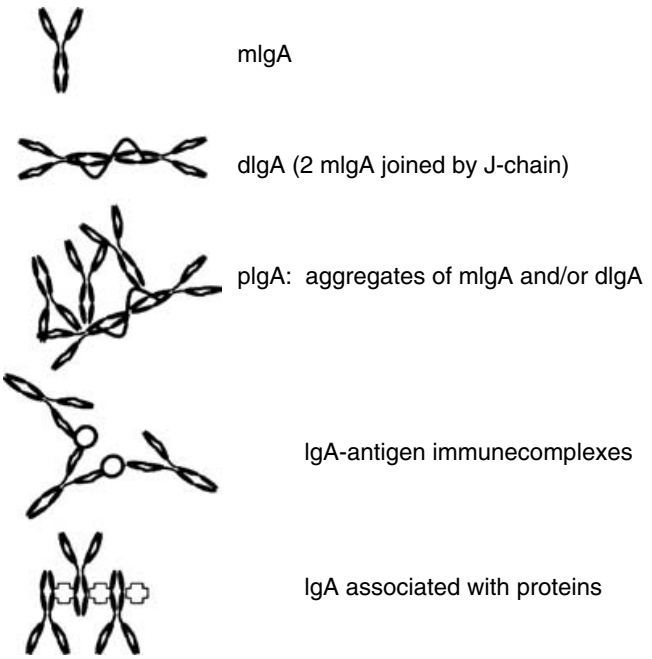

Fig. 1. Schematic representation of different forms of immunoglobulin A (IgA) in the circulation. Serum IgA consists of monomeric IgA (mIgA),dimeric IgA (dIgA), which includes two mIgA joined by J chain) and polymeric IgA (pIgA). Although mIgA and IgA have a well-defined molecular composition, pIgA may be present as mIgA and/or dIgA containing aggregates or immune complexes or IgA associated with other proteins.

human IgA displays unique heterogeneity in its molecular forms, each with a characteristic distribution in various body fluids. Circulating IgA is almost all produced in the bone marrow and contains approximately 90% IgA1 and 10% IgA2. Its κ/λ light chain ratio varies between 1.3 and 1.55 in different studies [13, 14]. It exists predominantly in the monomeric form with a small proportion as macromolecular IgA, which consists of dimeric IgA (dIgA) and polymeric IgA (pIgA). dIgA consists of two monomeric IgA units joined by the bridging protein J chain. The precise composition of pIgA is still unknown. These IgA-containing complexes might be aggregates of IgA, IgA containing immune complexes or complexes of IgA associated with other proteins (see Fig. 1). The IgA found in secretions, termed secretory IgA (sIgA), is predominantly dimeric in form. At mucosal sites dIgA is specifically bound by the pIg receptor (pIgR) on the basolateral surfaces of the mucosal epithelium, transcytosed through the epithelial layer, and released into mucosal secretions as covalent complex of dIgA and the cleaved pIgR ectodomain (secretory component).

Serum IgA in IgAN

Levels of plasma IgA1 are elevated in about half of the patients with IgAN [15–17], which appears to be the result of an increased production of this isotype by the bone marrow [18–21] and by a low elimination rate of the liver. This increase is restricted to the IgA1 subclass [17] with a predominance of λ light chains [13, 14]. Further increased circulating IgA-containing complexes are present in patients with IgAN. The elevated plasma levels of IgA1 and/or IgA1-containing immune complexes alone are not sufficient to cause mesangial deposition of IgA1. This is witnessed by the rare occurrence of IgAN in patients with IgA1 myeloma or infection with the human immunodeficiency virus (HIV) type I, which diseases are also characterized by high circulating IgA1 or IgA-containing complexes [22]. Although in children with IgAN circulating macromolecular IgA levels correlate with bouts of macroscopic hematuria [23, 24], in adults the correlation with disease activity is less clear [25].

O-glycosylation of IgA

The majority of serum proteins are glycoproteins. Sugars are attached to proteins as N-linked sugars (connected to asparagine residues) or O-linked sugars (connected to serine and threonine residues). The human IgA1 molecule is one of the few serum glycoproteins which possesses O-linked oligosaccharide (O-glycan) side chains in its hinge region [26, 27] (see Fig. 2). There are nine potential O-glycosylation sites (five Ser and four Thr) in each IgA1 hinge peptide, causing a variable number of O-glycan side chains [28]. The fundamental structure of the O-glycans is the linkage between the α-anomeric carbon atom in N-acetylgalactosamine (GalNAc) and the hydroxy group of serine or threonine [GalNAc-O-Ser (Thr)]. The GalNAc residue in the glycans of the human IgA1 hinge may be extended with β1,3-linked galactose (Galβ1,3GalNAc). Further, sialic acid [(N-acetylneuraminic acid (NANA)] could bind to galactose through an α2,3 link and to N-acetyl galactosamine (GalNAc) through an α2,6 link. Therefore, there could be several varieties of O-glycans structures in the hinge region of IgA1. In one study it was found that O-glycans were located at Thr228, Ser230, and Ser232, while O-glycan sites at Thr225 and Thr236 were partially occupied in the hinge peptide [27].

Several studies have shown that there is a defect in galactosylation of serum IgA1 from patients with IgAN [29–32]. An increased binding of GalNAc-specific lectins to serum IgA1 in IgAN was found, suggesting the undergalactosylation of the IgA1 hinge glycopeptides. This abnormal O-glycosylation has been confirmed by more precise analytic methods, including fluorophore-assisted carbohydrate electrophoresis [33] and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [34]. Further, Gal-deficient IgA1 was only found in the circulation of Henoch-Schönlein purpura patients in the presence of a clinical nephritis [35]. The underlying defect resulting in reduced galactosylation of the

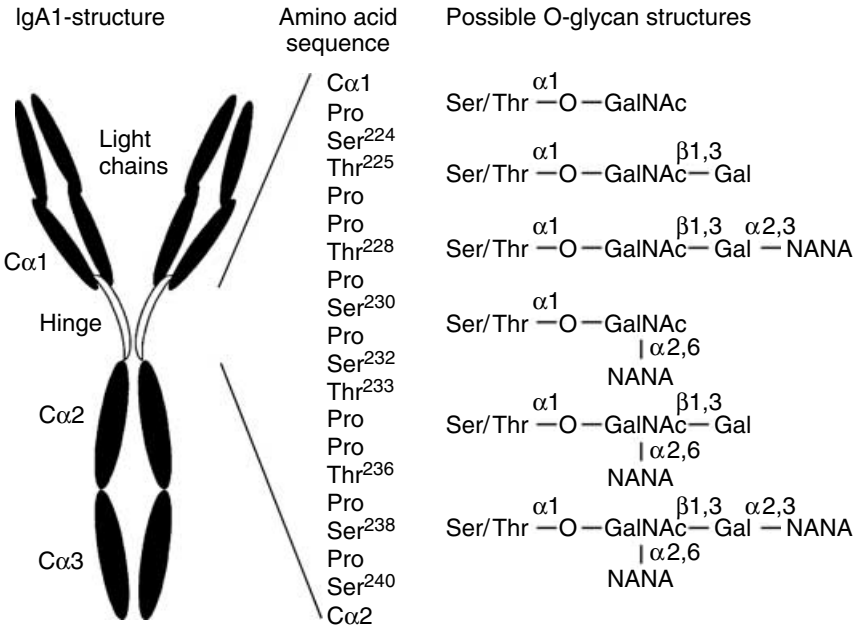

Fig. 2. Structure of immunoglobulin A (IgA1) and the amino acid sequence in the hinge region and possible O-glycan structures. Each IgA1 hinge region possesses nine O-linked oligosaccharide (O-glycan) side chains (five serine and four threonine). The hydroxy group of serine or threonine is linked to the α-anomeric carbon atom in N-acetylgalactosamine (GalNAc). The GalNAc residue may be extended with β1,3-linked galactose (Gal). Further, N-acetylneuraminic acid (NANA) (sialic acid) could bind to Gal through an α2,3 link and to GalNAc through an α2,6 link.

O-linked glycans of the IgA1 hinge region is still unknown. Galactosylation of O-linked glycans is performed by the intracellular enzyme β1,3 galactosyltransferase. A reduced expression or function of this enzyme may be involved [31]. In a single study a reduced activity of this enzyme was found in circulating B cells in patients with IgAN [36]. Further, in a mouse model an altered balance between Th1 and Th2 lymphocytes has been proposed as explanation for abnormal glycosylation of IgA [37].

Altered O-glycosylation might favor self-aggregation of IgA1 [38] and formation of circulating IgA-containing immune complexes [39]. There is also evidence for increased binding of abnormally O-glycosylated IgA1 to extracellular matrix (ECM) components [38, 40]. These aspects will be discussed later.

CIRCULATING IMMUNE COMPLEXES

The glomeruli in IgAN are characterized by diffuse and generalized mesangial deposition of IgA, usually accompanied by deposition of the C3 component of complement, and variable codeposition of IgG, IgM, or both. These IgA deposits may be derived from circulating immune complexes, suggesting an immune complex pathogenesis for the mesangial IgA deposits. IgA-immune complex levels may increase after food ingestion both in patients with IgAN and healthy controls. Although most studies are not controlled for food intake, elevated levels of IgA1 and IgA1 containing circulating immune complexes are elevated in sera of most IgAN patients [41–43]. Various techniques, like the conglutin test [41], solid-phase enzyme-linked immunosorbent assays (ELISAs) [43], and binding tests to solid-phase anti-C3 [42] have been used. However, these assays do not distinguish between true antigen antibody complexes and other forms of macromolecular IgA.

To obtain conclusive evidence for an immune complex pathogenesis, it should be demonstrated that the same antigen and/or antibody present in circulating immune complex is present in glomeruli. An association between the classes of immunoglobulins in circulating immune complexes and those in glomerular deposits in patients with IgAN has been reported [44]. Further IgA1 is predominantly present in both IgA-containing circulating immune complexes [41, 42] and in mesangial deposits [45] in patients with IgAN. Additional results suggesting that immune deposits originate from circulating immune complexes includes the presence of Gal-deficient IgA1 in both circulating immune complexes [32, 39, 46] and mesangial deposits of patients with IgAN [47, 48].

IgA1-IgA1 and IgA-IgG immune complexes

Removal of carbohydrates from the IgA1 molecule results in noncovalent self-aggregation [38]. Therefore underglycosylation of IgA1 in IgAN may lead directly to formation of IgA1-IgA1 complexes. Further, incomplete galactosylation of O-linked glycans in the IgA1 hinge region may result in the exposure of underlying neoantigenic GalNAc [32, 39]. This neoantigen may be recognized by naturally occurring antibodies (IgG or IgA1 specific for GalNAc) and lead to formation of circulating immune complexes [39]. The presence of antibodies bound to GalNAc residues in the hinge region reduces the hepatic clearance of the circulating immune complexes, which results in higher levels [39]. These circulating immune complexes are found to bind better to mesangial cells compared to circulating immune complexes from

healthy controls [46]. IgA rheumatoid factors has been described in 50% of patients with IgAN, but a correlation between IgA rheumatoid factor and the presence of IgG in glomerular deposits was not present [49].

IgA fibronectin complexes

Although complexes of IgA with fibronectin are found to be increased in patients with IgAN, the pathogenic role or diagnostic value of these increased levels remains doubtful [50–52]. The specificity of assays to detect IgA fibronectin complexes has been controversial [51–53] and high levels of IgA fibronectin aggregates are also found in patients with Henoch-Schönlein purpura without renal involvement and patients with cirrhotic liver disease in the absence of urinary abnormalities [51]. Elevated IgA fibronectin levels may be only a reflection of raised serum IgA levels. Recently, a 43 kD carboxy-terminal fragment of fibronectin was detected only in serum samples of patients with IgAN [54], but its pathogenic role in IgAN is still unknown.

Uteroglobin is an anti-inflammatory protein, which interferes with IgA fibronectin interaction. Recently, uteroglobin-deficient mice were generated. These mice showed features of human IgAN with glomerular deposition of IgA, C3, fibronectin, and collagen [55]. Further, these mice developed hematuria and a nephrotic syndrome progressing to renal insufficiency. It was hypothesized that due to the absence of uteroglobin, an excess of IgA fibronectin complexes were formed and deposited in the mesangial area. However, in a recent study [56] circulating uteroglobin levels were found not to be reduced in patients with IgAN, suggesting that another pathogenesis of mesangial IgA depostition may occur in patients with IgAN as compared to uteroglobin-deficient mice.

Dietary and microbial antigen containing immune complexes

In many studies one has searched for antigens that may be responsible for immune complex formation. Although serum antibodies to both dietary antigens and various infectious agents have been identified in patients with IgAN, no consistent antigen associated with mesangial IgA deposition was identified.

Other circulating IgA-containing complexes

Recently, it has been suggested that the IgA receptor FcαRI/CD89 may contribute to formation of pIgA [57] and play a role in the pathogenesis of IgAN [58]. This IgA receptor is a type I receptor glycoprotein, expressed on myeloid cells. Cross-linking of CD89 triggers diverse processes, including phagocytosis, superoxide generation, antibody-dependent cellular cytotoxicity, and release of inflammatory mediators. Further, the FcαRI/CD89 receptor has been reported to play a crucial role in the clearance of IgA complexes [59, 60]. Upon activation, a soluble form of CD89 is released from the surface of monocytes and monocytic cell lines [61]. These soluble CD89 molecules circulate in a complex covalently linked with IgA in the high-molecular-mass fractions of serum IgA [57]. These high-molecular-mass complexes of CD89 IgA can be distinguished from J chain containing dIgA and it has been hypothesized that J chain and CD89 are competing for the same cysteine. In analogy with the pIgR system, we suggested that the mechanism of covalently linkage of IgA to CD89 is most likely, that reshuffling of cysteine bonds takes place in an intracellular compartment [57]. When the covalently linked IgA CD89 complexes are released, they circulate in the high-molecular-mass fractions of serum IgA, suggesting that CD89 might contribute to the formation of serum pIgA [57]. Two soluble forms of CD89 have been reported in human serum: a highly glycosylated 50 to 70 kD protein, which was found to be elevated in polyethylene glycol (PEG) serum precipitates from patients with IgAN [58] and a 30 kD protein, which does not seem to be specific for IgAN [62]. In the first study, soluble CD89 IgA complexes were found only in the circulation of patients with IgAN and transgenic mice expressing human CD89 on monocytes/macrophages spontaneously developed a picture compatible with IgAN [58]. Therefore, a pathogenic role for IgA CD89 complexes in IgAN has been suggested. However, CD89 was not detectable in renal biopsies. Recently, we found that serum levels of IgA CD89 complexes were not increased in patients with IgAN compared to healthy controls [62]. These data strongly suggest that CD89 can circulate in different molecular forms. Therefore, additional studies are required to further analyze the role of IgA CD89 complexes in IgAN.

IGA IMMUNE RESPONSE

The presence of a clinical association between exacerbations of the disease and upper respiratory tract infections suggests a relation between the mucosal immune system and the deposition of IgA in the renal mesangium. Increased numbers of pIgA1-producing cells in both tonsils [63] and bone marrow [18, 21, 64] and increased serum IgA levels suggested a state of hyperresponsiveness. However, IgA and IgA subclass concentrations in mucosal secretions have been found to be similar in patients with IgAN as compared to healthy subjects [25]. A deficient primary mucosal immune system was found and it was hypothesized that this deficient primary immune response might lead to recurrent mucosal infections and persistence of the antigenic stimulus in patients, whereas healthy individuals succeed in the elimination or exclusion of the antigen by a more effective mucosal immune response [25]. The resulting ongoing or repeated

stimulation of the immune response in IgAN patients may eventually lead to appropriate protection at the mucosal level. However, as a consequence an increased number of antigen-specific B cells are generated, resulting in a overproduction of IgA1 antibodies in the systemic compartment [25]. It has been found that macromolecular IgA in serum is especially increased in the acute phase of the immune response [12]. Infection or immunization (parenteral or mucosal) with nonviable or live vaccines induces the synthesis of antigen-specific macromolecular weight IgA in the initial phase of the immune response. In chronic viral or bacterial infections a shift has been found to monomeric IgA in the chronic stage of the disease [12]. Therefore, systemic macromolecular IgA levels may reflect the phase of the systemic IgA immune response. An exaggerated systemic IgA response to chronic mucosal infections was confirmed in another study [65]. Patients with IgAN with infections caused by *Helicobacter pylori* had markedly elevated systemic levels of IgA anti-*H. pylori*, which was predominantly IgA1 and polymeric of nature. Traffic of lymphocytes plays an important role in the link between the mucosal and systemic IgA system [25]. Further studies are required to examine whether a relocation of mucosal lymphocytes to systemic sites may explain the increased systemic IgA response to mucosal infections [65].

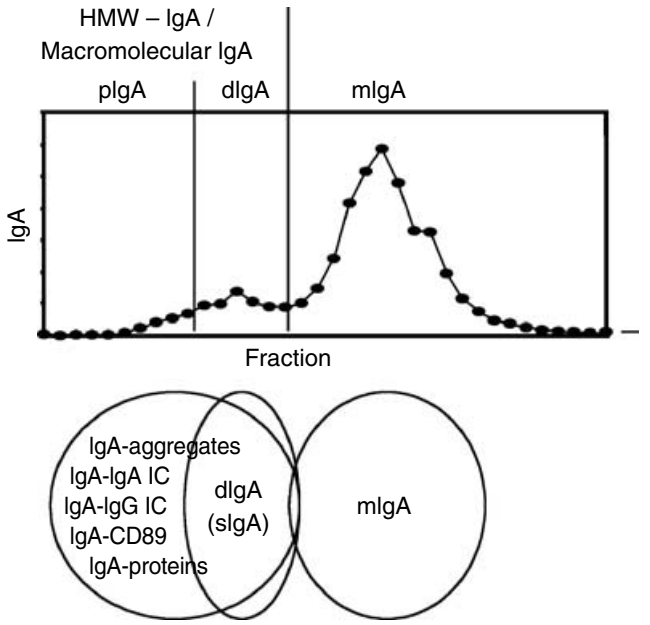

Fig. 3. Molecular composition of serum immunoglobulin A (IgA). Size fractionation of human serum shows the presence of monomeric IgA (mIgA), dimeric IgA (dIgA) and polymeric IgA (pIgA). High-molecular-weight IgA (HMW-IgA) or macromolecular IgA has been defined as the dimeric and polymeric IgA fractions together (upper part of figure). Aggregates of IgA, IgA-containing immune complexes, or complexes of IgA associated with other proteins may be present in both dimeric and polymeric fractions (lower part of figure).

MESANGIAL IGA

Mesangial IgA has been found of the IgA1 isotype [45, 66], although also the presence of IgA2 in renal biopsies has been reported [67]. Its light-chain composition is predominantly λ IgA [68]. Although increased serum levels of IgA1 [15–17] and λ IgA [13, 14] have been found in patients with IgAN, their pathogenic role is still unknown. Secretory component has rarely been identified in renal biopsies, suggesting a systemic origin of mesangial IgA.

Presence of macromolecular IgA in mesangium

Mesangial IgA has been found to consist at least in part of macromolecular IgA [9, 10]. Methods used to demonstrate the polymeric nature of mesangial IgA are analysis of the capacity to bind free secretory component or demonstration of the presence of J chain in renal biopsies. However, both techniques are hampered that not only dIgA, but also codeposited IgM contains J chain and can bind noncovalently to free secretory component. Several groups have performed binding studies to free secretory component in renal tissue of patients with IgAN, Henoch-Schönlein purpura, systemic lupus erythematosis (SLE), and alcoholic liver disease (ALD) [9, 66, 69–71]. In renal biopsies of patients with IgAN, the presence of binding to secretory component varied from 10% to 100% [66, 69].

Studies demonstrating the presence of J chain have been hampered by the poor specificity of some anti-J chain antibodies. J chain was present in most patients with IgAN [10, 66, 69, 72, 73]. In some of the biopsies J chain was present in the absence of IgM. It has to be realized that binding to secretory component and/or the presence of J chain in renal biopsies does not mean that immune deposits are predominantly constituted of pIgA. The results are obtained with qualitative techniques and suggest only that mesangial IgA consists at least in part of dIgA. These studies do not provide evidence concerning the presence of pIgA in renal biopsies. However, in one mentioned study [9] eight eluates were analyzed under nondissociating conditions (pH 6.8) and five eluates were subjected to chromatography under acidic conditions (pH 3.5). Under neutral and acid conditions, 52% and 69%, respectively, of the eluted IgA had a molecular weight ≥320 kD. Eluates that were radioactively labeled and fractionated by sucrose density gradient ultracentrifugation showed a peak in the high-molecular-weight range in three out of five patients examined [10].

Glycosylation of mesangial IgA

When the charge of eluted IgA, obtained from renal biopsies of five patients, was analyzed by isoelectric focusing on agarose, the eluated IgA was found to be

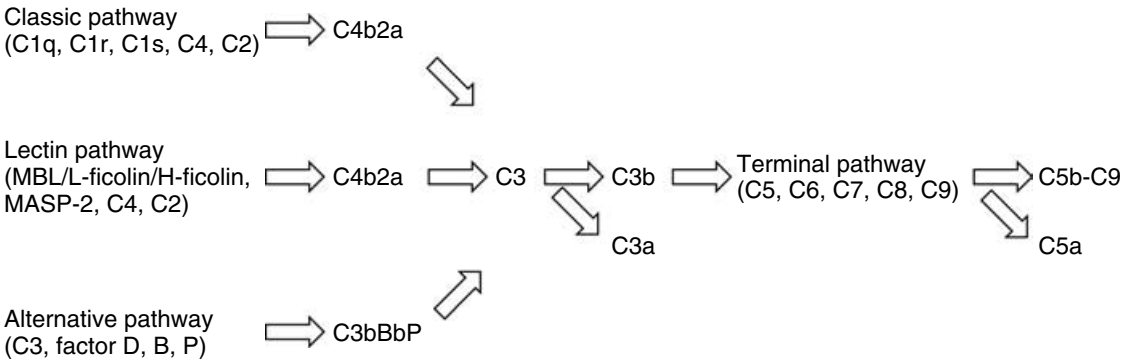

Fig. 4. The three pathways of complement activation. Each complement-activation pathway generates a C3 convertase (C4b2a/C3bBbP), which mediates cleavage of C3, followed by activation of the terminal complement pathway and formation of the membane attack complex.

predominantly anionic, which might be related to abnormal glycosylation [9]. In another study [48], IgA1 was obtained from 290 renal biopsy specimens of patients with IgAN. Analyzing the pooled IgA by mass spectrometry, a reduced O-glycosylation of the glomerular IgA was found. In a third study [47], IgA1 was eluted from glomeruli from three kidneys, obtained after nephrectomy or postmortem. Binding of the eluted IgA1 to lectins, specific for terminal GalNAc, was markedly higher as compared to serum IgA1, suggesting that abnormal O-glycosylated IgA1 molecules are more likely to deposit in the kidney.

MESANGIAL IGA DEPOSITION

The mechanism leading to mesangial IgA deposition is still unknown. There is no direct evidence to suggest that the deposited IgA is directed against specific glomerular antigens. Although IgA may bind to receptors or ECM proteins, other mechanisms like binding of associated proteins in IgA-containing complexes, may also be an option. Many investigators have studied direct interactions of serum IgA with mesangial cells and matrix components. Until now, several IgA receptors have been identified on several cell types: the hepatic asialoglycoprotein receptor (ASPGR), the myeloid FcαRI/CD89 receptor, the pIgR on epithelial cells in the mucosa, the Fcα/μ receptor on the majority of B lymphocytes and macrophages, and the recently as IgA receptor described transferrin receptor [74–78]. In addition, poorly characterized IgA-receptors have been reported on various cell types [46, 79–82]. Studies from several groups have now excluded the asialoglycoprotein, the FcαRI/CD89 and the pIg receptor as mesangial cell IgA receptor [46, 79, 82–84]. Although mesangial cells express mRNA for the Fcα/μ receptor [85], IgA1 binding to mesangial cells was not inhibited by IgM [79], suggesting a less important role for this receptor concerning mesangial IgA deposition. Expression of CD71 mRNA (transferrin receptor) by proliferating mesangial cells was recently confirmed [46]. CD71 binds pIgA1 and has a higher avidity for underglycosylated IgA1 and IgA1 complexes than normal IgA1 [76, 86]. Characterization of other IgA receptors on mesangial cells requires additional attention. The Fc portion of the IgA1 molecule probably mediates binding of IgA1 to mesangial cells, because both intact IgA1 and the Fc portion, but not its Fab fragment inhibits binding of IgA1 to mesangial cells [46, 79]. Underglycosylation of IgA may lead to selfaggregation and formation of IgA1-IgA1 and IgA1-IgG immunecomplexes. Macromolecular IgA binds better to mesangial cells as compared to monomeric IgA. It is not quite clear what the impact is of the abnormal glycosylation of IgA concerning this increased binding of macromolecular IgA to mesangial cells. Recently, it was found that Gal-deficient pIgA1 myeloma protein bound better to mesangial cells as compared to unmodified pIgA1 myeloma [46]. However, circulating immune complexes containing aberrantly glycosylated IgA from patients with IgAN bound even better [46], suggesting that not the abnormal glycosylation alone, but additional factors also play a role in the binding of pIgA to mesangial cells. Although binding of IgA to mesangial cells might be mediated by IgA receptors, some investigators found that the adhesion activity of serum IgA to ECM proteins, such as type IV collagen, fibronectin, and laminin was significantly increased in patients with IgAN [22, 40, 87, 88]. Since removal of carbohydrates from the IgA1 molecule resulted in a significant increase in adhesion to ECM proteins [38], underglycosylation of the IgA molecule as observed in IgAN may play a role.

After binding of IgA to mesangial cells a number of events can be triggered. In vitro studies have demonstrated an enhanced proliferation [89, 90], increased cytokine release [89–91] and enhanced production of ECM [92]. In IgAN mesangial IgA deposits may be accompanied by IgG and/or IgM and C3, but the C1q component of complement is rarely found. It is generally accepted

that IgA does not activate the classical pathway of complement [93]. Activation of the alternative complement pathway by IgA is supported by both in vitro and in vivo observations [94–97]. Recently, it was shown that the complement system can also be activated by human IgA via the lectin pathway, which is mainly driven by mannan-binding lectin (MBL) [93]. In Figure 4 the three pathways of complement activation are shown. Activation of the lectin pathway in the renal mesangium is supported by deposition of MBL and MBL associated serine protease (MASP-1) in association with IgA in the mesangial area of patients with IgAN [98, 99] and patients with Henoch-Schönlein purpura [100]. Therefore, activation of complement in the renal mesangium by IgA may be mediated by both the alternative and lectin pathway. Activation of both pathways is most prominent for pIgA [95, 96, 101]. Therefore, deposited pIgA most likely contributes to the development of renal damage by complement and mesangial cell activation. This mesangial damage may be enhanced by underglycosylation of mesangial IgA. GalNAc and Gal-exposing glycoforms isolated from patients with IgAN showed more alternative complement pathway activation than controls [102]. Furthermore, it was found that abnormally glycosylated IgA was able to modulate human mesangial cell functions like integrin expression and vascular endothelial growth factor (VEGF) synthesis [103]. Whether the binding of IgA molecules and components of the lectin pathway like MBL, MASP, and ficolin are influenced by alterations in glycosylation of IgA still has to be elucidated.

CONCLUSION

The precise origin and nature of mesangial IgA deposits in IgAN remain uncertain. The mesangial IgA deposits contain at least in part macromolecular IgA and may be derived from circulating immune complexes. Searching for responsible antigens for these immune complexes has not resulted in the identification of a consistent antigen. The basic abnormality in IgAN lies most probably within the IgA immune system rather than in the kidney. A deficient primary mucosal immune system may result in an exaggerated systemic IgA response, which results in elevated levels of serum IgA, which is predominantly IgA1 and polymeric of nature. Since increased IgA production alone is not sufficient to develop IgAN, physicochemical properties of circulating IgA are likely to play a role. This is supported by the presence of altered glycosylation of serum and mesangial IgA in patients with IgAN. Undergalactosylated IgA containing complexes bind better to mesangial cells as compared with circulating complexes of healthy controls. Complement activation by (polymeric) IgA via the alternative and lectin pathway may contribute to renal damage.

ACKNOWLEDGMENT

Parts of these studies were supported by a grant from the European Union (QLG1-CT2002-01215).

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